Oath/Declaration

The Examiner rejected the declaration on the basis that it does not identify the application number and filing date. A copy of the declaration that was filed is enclosed. The application number and filing date were clearly indicated therein.

The Examiner rejected the oath and declaration on the basis that it does not state whether the inventor is a sole or joint inventor of the invention claimed. The form enclosed with the invention (USPTO FORM PTO/SB/01A, approved for use by USPTO to October 3, 2002) complies with the requirements of the new patent rules, as the form is the form provided by the USPTO. If one inventor is named and signs the declaration, it is assumed that they are the sole inventor. As such it is requested that the Examiner accept the declaration as is and waive any requirement for affirming that the inventor is the sole inventor of the invention claimed, when it is self evident by the document that this is so.

In any event a newly executed declaration is enclosed affirming that Malcolm King is the sole inventor for the present invention.

Double Patenting

The Examiner rejected claims 1-3, 7-10, 12-18, 20, 22, 24-27 [Note office action states 34-27, however we believe 24-27 was intended as there are only 28 claims on file.], on the basis that the copending Application No. 09/052614 ('614) claims are not patentably distinct from those of the present invention. As requested by the Examiner, enclosed is a copy of the claims as on file in the '614 application that were previously forwarded to the Examiner on May 15, 2001.

Applicant cannot agree. The claims of the '614 and the present application are patentably distinct.

In order to be patentable, the invention has to be novel, non-obvious and have utility. The '614 application describes the use of "neutral" dextran" for improving mucus clearance. This is supported by the specification where at page 7, line 5, dextran is defined as a "neutral polymer". A neutral dextran is also used in the Examples of the '614 application. This differs from the present invention, which describes the use of "charged" dextran for improving mucus clearance from the respiratory tract of a patient. It is well known in the art that a neutral molecule will have different properties than a 'charged" or 'non-neutral" molecule; thus the teaching of the use of a neutral molecule in having a certain effect would not necessarily or also encompass or imply the teaching of the use of the charged or "non-neutral" molecule. The hydrogen bonding sites of the dextran sulfate interacts with the hydrogen bonds of the mucous glycoproteins, similar to the case with neutral dextran. However, in addition, dextran sulfate reduces the interactions between the positively and negatively charged moieties in the mucins through an electrostatic shielding mechanism. The latter interaction is not possible with neutral dextran. As such the claims of the present invention are novel.

The claims of the present invention are non-obvious from the '614 application. The test for obviousness is whether the invention would have been obvious to a person of ordinary skill in the art to which the subject matter of the invention pertains at the time of the invention in the light of the teachings of the prior art.

To establish a case of obviousness in such a situation, it is required to find some motivation or suggestion to make the claimed invention in light of the prior art teachings and in light of person of ordinary skill in the art. There is no express or implied teaching in the '614 patent application that a "non-neutral" dextran can be used in the invention. The '614 application specifically defines dextran as a "neutral molecule". There is no

motivation in the '614 patent application to use charged dextrans. At the very least, the use of charged dextran in the present invention is a novel selection or improvement over the '614 application and is independently novel and non-obvious.

The present inventor has found that charged dextran had a much stronger effect on decreasing mucus viscoelasticity and in improving mucus clearability than neutral dextran *per gram*, and furthermore its effectiveness at reducing viscoelasticity was much more prolonged, lasting more than an hour after inhalation. The fact that dextran sulfate disrupts both hydrogen bonds between oligosaccharides present in the mucus and ionic interactions therein was stated in the present application to account for this improved effectiveness. Neutral dextran only works to disrupt the hydrogen bonds of oligosaccaharides. [See pp 3 and 11 of the application]. The application states that surprisingly dextran sulfate is more effective than neutral dextran in improving mucus clearance and in descreasing viscoelasticity of the mucus. Thus, although neutral and charged dextran have the same base sugars, they work in different ways. It is not only the base structure that is important in its effectiveness but also the charge and ionic distribution. This is shown in the present application.

There is nothing in the '614 patent application that would teach a person of ordinary skill in the art to use dextran sulfate or a charged dextran over a neutral dextran or that it would be better at improving mucus clearance from the respiratory tract of a patient, than neutral dextran. Thus the invention of the present application is both novel and non-obvious in light of the '614 patent application, irrespective of any issues of common inventorship or ownership.

35 USC § 112

Claims 1,7 and 20 were rejected by the Examiner on the basis that the following terms were indefinite: "decreasing" and "improving". Applicant cannot agree. It is clear that

these terms in the present context are sufficiently clear. It is submitted that a person skilled in the art would have no problem in understanding that the term "decreasing viscoelasticity of respiratory tract mucus" would mean any decrease in viscoelasticity of the mucus from any starting level. Similarly with the term "improving", any improvement of mucus clearance from a starting level. This would be determined by the ability of a patient to eject mucus from their respiratory tract. The terms would be understood by a person of ordinary skill in the art to have their plain dictionary meaning. It should be noted that even healthy animals and healthy humans can have their mucus clearance accelerated by a decrease in mucus viscoelasticity, further improving mucus clearance or decreasing mucus viscoelasticity even beyond the normal could be of use in compensation for other defects, such as abnormal function of the cilia.

35 USC § 102

Claims 20-26 are rejected under 25 U.S.C. 102(b) as being anticipated by Speert et al (US Patent No. 5,514,665, that discloses dextran sulfate pharmaceutical compositions comprising dextran having a molecular weight of 3,000 to 1,000,000. Applicant has cancelled these claims without prejudice, especially without prejudice to any right to pursue such claims in a subsequent divisional or continuation application.

35 USC § 103(a)

Claims 1-3, 7-10, 12-18, 20, 22, 24-27 [the office action stated 34-37, but it is submitted that this was in error as there are only 28 claims on file] were rejected on the basis that they are obvious in light of co-pending application no. 09/052614. Applicant cannot agree. This is a similar rejection as that made regarding double patenting and the same arguments apply here. As such the Examiner is requested to withdraw the rejection in light of the submissions provided above.

Further the claims are not obvious in light of the '614 patent application alone or in light of the references cited by the Examiner below, individually or collectively. The only

reference cited by the Examiner that described the use of dextran sulfate, albeit for a use that is different than the present invention, is the Speert reference. It should be noted that new methods of use of an old compound are patentable, ie., the prior use of a compound for a particular purpose does not render a claim to a method of use of that compound for a different purpose obvious.

Further, Speert teaches away from the use of dextran sulfate, especially low molecular dextran sulfate in pharmaceutical compositions. At col.5, lines 31-36, and 45-56 and col. 6, lines 45-63, Speert states that dextran sulfate of 8,000 to 1,000,000 would work their invention, but it is not preferred due to various potential toxic effects and that hydrogenated dextran (known as dextran) are preferred. The present inventor in Example 1 has shown the safety of the use of dextran sulfate. It was found dextran sulfate to be safe for repeated administration.

The Examiner rejected claims 1-28 as being obvious in light of Speert et al. (5,514,665), Ahmed (5,980,865) and King et al. (1998). Applicant cannot agree.

Speert et al. teach the effect of dextran sulfate (3,000 – 1,000,000 MW) on the adhesion of P. aeruginosa bacterial cells and in the prevention and reducing the risk of such infections in patients, such as those having cystic fibrosis, wherein it is a common infection. Speert states that the invention is for the use of dextran (hydrogenated form of dextran/dextran sulfate or dextran sulfate to reduce adhesion of bacterial pathogens, P. aeruginosa, to human respiratory epithelial cells. Thus the dextran sulfate can be used to reduce risk or prevent such infections (either initially, or in preventing recolonization of the bacteria). Speert does not teach the treatment of the infection per se. One would have to use an antibiotic to actually treat the infection.

As stated by the Examiner at page 5 of the office action, Speert fails to teach a method of clearing mucus, methods of diagnosing and methods of determining dosage. There is

no teaching in Speert to use dextran sulfate to decrease viscoelasticity of mucus or to improve mucus clearability in a patient in need thereof as is the teaching of the present invention. Speert does not teach physically interfering with chemical bonds present in mucus to decrease the viscoelasticty thereof and mucus clearability. As such, Speert does not teach a person of ordinary skill in the art to administer dextran sulfate in situations where one requires improvement of mucus clearability, nor in any situations in which infection by a bacterial pathogen is not an issue. For instance, cystic fibrosis is a genetic disease that causes the body to produce an abnormally thick, sticky mucus, due to the faulty transport of sodium and chloride (salt) within cells lining organs such as the lungs and pancreas, to their outer surfaces. It is not caused by bacterial pathogens. [See Quinton PM. Physiological basis of cystic fibrosis: A historical perspective. Physiological Reviews 1999; 79 (Suppl 1): S3-S22 enclosed.] Cystic fribosis patients may be more susceptible to bacterial infections, but treating or preventing these infections, would not address their underlining chronic problem of production of mucus or mucus clearability. A physician, in light of Speert alone or in combination with the King and Ahmed references, would not administer it to a patient for this purpose. Thus Speert does not teach or suggest the use of dextran sulphate as claimed in the present invention. It should be noted that the new method of use of an old compound is patentable subject matter.

King et al. describes the use of low molecular weight heparin in reducing the viscoelasticity of human CF sputum and healthy dog mucus. It does not disclose or suggest the use of dextran sulfate to reduce the viscoelasticity of mucus. Nor does it disclose the improved use ofdextran sulfate in reducing the viscoelasticity of mucus and in improving mucus clearablity.

First the structure of dextran (a polysaccharide with a poly- alpha-D-(1-6)-Glucose with periodic (1-3) branch points to alpha-D-Glucose oligosaccharides) is "loose jointed" and as such differs greatly in structure from other unsubstittued polysaccharidee such as

glyosaminoglycans in which heparin is a member. Even in relation to other 1-6 linked polysaccharides, the conformational aspects of dextran which provide the desired activity cannot be assumed for other like polysaccharides because of the "loose jointed" nature of these class of polysaccharides. Thus one cannot necessarily predict the applicability of the effect of heparin seen in King to dextran sulfate. Even if a person of ordinary skill in the art were to look at Speert, it is submitted that one would not have been inclined to use dextran sulfate in a pharmaceutical application, nor would they be motivated to use a low molecular weight dextran sulfate, especially in light of the teachings of Speert that states it is not preferred. As stated above, Speert states the use of dextran sulfate is not preferred and is taught away from due to potential side effects. Even if it were used, Speert states that a higher molecular weight dextran sulfate (8,000 to 1,000,000) should be used. [See comments above.] Nor would one combine the teachings of King with Speert to use dextran sulfate to decrease mucus viscoelasticity as there is no common nexus between the two cited references (application or compounds).

Last, it should be noted that the present inventors have surprisingly shown that dextran sulfate is a much better at improving mucus clearability than heparin (See Example 2 and Figure 5). This was not suggested, nor could it have been predicted by King. No one would have anticipated this enhanced effect on mucus viscoelasticity and mucus clearance. Speert adds nothing to this argument, as Speert et al, does not disclose or teach the use of dextran sulfate for the purpose of the present invention nor does it provide any comparison of the effectiveness between heparin and dextran sulfate that would suggest any enhanced pharmaceutical effect of dextran sulfate over heparin.

Ahmed describes a method of treating a mammalian patient for late phase allergic reactions or inflammatory reactions, including bronchial hyperactivity and asthma using low molecular weight (1000-3000) heparin. The mechanism used to treat an inflammatory reeponee ae deecribed in Ahmed, ie., to suppreee inflammatory response,

is very different from what is taught in the present invention, i.e. to physically break up mucus. There is no suggestion in Ahmed to use heparin to decrease mucus viscoelasticity or improve mucus clearance. One would not be motivated to use dextran sulfate for the purpose of Ahmed. At col . 10, lines 39-52 ofAhmed, it is stated that the invention may also encompass the use of sulfated polysaccharides derived from heparan sulfate, dermatan sulfate, chondroitin sulfate, pentosan polysulfate and/ or other glycosaminoglycans and mucopolysaccaharides. Dextran sulfate is not derived from any of the polysaccharides so mentioned, it is not a glycosaminoglycan and is not a mucopolysaccharade. Mucopolysaccharides are proteoglycans, complex molecules found in every tissue of the body (see US patent no. 6,153,187, col. 4, lines 34-40).

Even if one were motivated, which we submit they would not, to use dextran sulfate for the applications disclosed in Ahmed, one would not expect or use it to decrease mucus viscoelasticity or improve mucus clearance. Nor would one combine Ahmed's use of heparin to treat inflammatory reactions with that of Speert, to use dextran sulfate in the method of the present invention, or to use low molecular dextran as in the present invention.

Thus Ahmed teaches the use of a different molecule from the present invention for a different purpose. One could not combine it with Speert and/or King to arrive at the present invention.

In conclusion, a new method of use of an old compound is patentable subject matter. This new method of use is not obvious from the prior art cited by the Examiner, as none of the references suggest or describe the use of dextran sulfate to physically break the bonds in mucus, to decrease viscoelasticity and improve mucus clearability. The unexpected improved use of a particular compound (dextran sulfate over neutral dextran and heparin), especially in light of the amount of prior art in this area that does not disclose an optimum solution to the problem of mucus viscolelasticity and

clearability should further support the patentability of the present invention. The Examiner is reminded that the use of hindsight is not to be used in assessing obviousness. As such it is submitted that the Speert, King and Ahmed references cited by the Examiner, either alone or in combination due not render the claims of the present invention obvious. The Examiner is requested to withdraw the rejections in light of the amendments and submissions made herein.

Additional Prior Art

Enclosed are two additional references that were cited against the application in corresponding New Zealand patent application, that the Applicants wish to place on file for consideration.

1. Beller et al, *Am. J. Obstet gynecol* 1986; 155:970 present two cases of psudomyxoma pertionei wherein the gelatinous mucus was biochemically analyzed. The mucus contained approximately 98% protein and 2% to 5% carbohydrtate per unit of dry weight. The predominant carbohydrate components were galactose and mannosamine. The mucus also had thromboplastic activity. Because of these findings, dextran sulfate at concentrations between 2% and 10% was instilled in to the abdominal cavity and caused lysis of mucus. However, although Beller et al are using the term "mucus, it is not mucus as commonly known by a person of ordinary skill in the art and it is not the same as respiratory mucus as used in the present application. Further, although Beller et al, used the term mucolytic treatment: in the titled of the article, they were not in fact treating mucus per se.

Mucus is a three-dimensional crosslinked gel formed from mucin macromolecules, which are approximately 80% carbohydrate, 20% protein by weight, containing the sugars galactose, N-acetylgalactosamine, N-acetylglucosamine, fructose and sialic acid [Thornton DJ et al, Structures and biochemistry of human respiratory mucins. Chapter 2 of Rogers DF et al, Airway Mucus Basic Mechanisms and Clinical Perspectives Basel:

Birkhauser, 1997: 19-39]. Mucins do not contain mannose or mannosamine residues, and mucin gels do not exhibit thromboplastic activity.

Also, Beller states they instilled dextran sulfate at up to 10% into the abdominal cavity to bring about lysis of the mucous-like gel, whatever it was. This is different from the present application which calls for aerosolizing dextran sulfate to the lungs to reduce the degree of crosslinking and improve mucus clearance.

2. Kennedy & Hoidal (WO 91/15216 – Method and medicament for prevention or medication of human leukocyte elastase mediated pulmonary diseases), describes primarily polysulfated polysaccharides as inhibitors of elastase mediated lung injury, such as that leading to the development of emphysema, and more specifically with polysulfated dextran. They propose a different mechanism of action than the present application, namely inhibition of the development of colonization sites for the bacteria by the proteolytic activity of elastase in the pulmonary tract. As discussed with Speert, this would result in a different application of use (e.g. it would be prescribed for a different use) than in the present invention.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

In view of the foregoing, it is submitted that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Should the Examiner like to discuss the matter, he is kindly requested to contact Anita Nador at 416-957-1684 at his convenience.

Respectfully submitted,

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"Version with markings to show changes made"

What is claimed is:

1. A method of decreasing viscoelasticity of respiratory tract mucus comprising administering to the mucus an effective amount of charged dextran.

2. The method of claim 1 wherein the charged dextran is a low molecular weight dextran.

3. The method of claim 2 wherein the molecular weight of the dextran is from 500 to 5000.

4. The method of claim 1 wherein the charged dextran is dextran phosphate or dextran sulfate.

5. The method of claim 4 wherein the charged dextran is dextran sulfate.

6. The method of claim 3 wherein the charged dextran is dextran sulfate.

7. The method of claim 1 for improving mucus clearance from the respiratory tract of an animal in need thereof comprising administering to the animal an effective amount of charged dextran.

8. The method of claim 7 for treating an animal with impaired mucus clearance.

9. The method of claim 8 wherein the impaired mucus clearance is associated with a lung disease.

10. The method of claim 9 wherein the lung disease is selected

from the group consisting of: cystic fibrosis, chronic bronchitis, brronchitis, bronchiectasis, bronchiolitis and bronchial asthma.

11. The method of claim 8 wherein the animal is a horse and the disease is heaves.

12. The method of claim 10 wherein the animal is human.

13. The method of claim 12 wherein the disease is cystic fibrosis.

14. The method of claim 7 wherein the effective amount is between about 39 mg to about 552.5 mg.

15. The method of claim 7 wherein the charged dextran is administered to the respiratory tract of the animal in the from of a pharmaceutical composition comprising a charged dextran and a pharmaceutically acceptable carrier.

16. The method of claim 15 wherein the pharmaceutical composition is an aerosol and is administered through inhalation.

17. The method of claim 16 wherein the charged dextran is low molecular weight charged dextran.

18. The method of claim 17 wherein the molecular weight of the charged dextran is from 500 to 5000.

19. The method of claim 18 wherein the charged dextran is dextran sulfate.

~~20. A pharmaceutical composition for decreasing the viscoelasticity of mucus comprising a charged dextran and a pharmaceutically acceptable carrier.~~

~~21. The pharmaceutical composition of claim 20 wherein the charged dextran is a low molecular weight dextran.~~

~~22. The pharmaceutical composition of claim 21 wherein the molecular weight of the charged dextran is from 500 to 5000.~~

~~23. The pharmaceutical composition of claim 22 wherein the charged dextran is dextran sulfate.~~

~~24. The pharmaceutical composition of claim 20 wherein the composition comprises between about 6.5 mg/ml to about 65 mg/ml of dextran sulfate/ml of the composition.~~

~~25. The pharmaceutical composition of claim 17 wherein the composition is a topical composition.~~

~~26. The pharmaceutical composition of claim 17 wherein the composition is an aerosol.~~

27. The method of claim 1 for diagnosing an animal with impaired mucus clearance comprising obtaining a sample of the animal's mucus and treating it *in vitro* with charged dextran, determining the effect of the charged dextran on the viscoelasticity of the mucus to determine whether the animal may have impaired mucus clearance.

28. The method of claim 1 for determining a dosage regime of an animal with impaired mucus clearance, comprising:

(a) obtaining a mucus sample from the animal;

(b) subjecting aliquots of the mucus sample to different concentrations of charged dextran;

(c) measuring the viscoelasticity of each of the aliquots of the mucus sample after adminstration of the charged dextran, and

(d) determining the preferred dosage of charged dextran based on comparing the effect of the different concentrations of charged dextran on the viscoelasticity of the mucus sample.